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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SLOBODYANSKY, ELIZABETH	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,446	PRZYBYLA ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-114* is/are pending in the application.

4a) Of the above claim(s) *88-111* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-87, 112-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/27/01; 7/23/01; 5/20/04*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed May 20, 2004 amending claims 48, 63, 64, 74, 75, 77-79, 83, 87 and 112 has been entered.

Claims 45-114 are pending. Claims 88-111 are withdrawn.

Claims 45-87 and 112-114 are under consideration.

Information Disclosure Statement

The year of the Menon et al. reference was corrected to "1997" on form PTO-1449 filed June 27, 2001, page 3. Therefore, this entry was lined through on form PTO-1449 filed May 20, 2004 as being a duplicate.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 45-51, 53-87 and 112-114 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 45-63, 65-81 and 112-114 are directed to or depend from a polynucleotide comprising a nucleotide sequence encoding a rubredoxin fusion protein

comprising an N-terminal rubredoxin constituent and a C-terminal fused polypeptide. Claims 64 and 82-87 are directed to or depend from a polynucleotide comprising a nucleotide sequence encoding a rubredoxin fusion protein comprising an N-terminal rubredoxin constituent and a C-terminal fused β-amyloid. Claims 46, 48 and 53 recite any proteolytic cleavage site whereas claims 48 and 54 recite any spacer located between rubredoxin and polypeptide.

Therefore, the claims are directed to a genus of nucleotides encoding fusion proteins of diverse structure and function. Said fusion proteins comprise a rubredoxin from any source and a variant thereof having any structure and any additional polypeptide sequence. The specification describes polynucleotides encoding fusion proteins comprising a single representative of rubredoxins, the *Desulfovibrio vulgaris* rubredoxin. Claims 64 and 82-87 limit the C-terminal polypeptide to β-amyloid peptide which in turn represents a genus of β-amyloid from any source both naturally occurring and man made having any structure and comprising all allelic variants of a human β-amyloid, for example. The members of the genus of fusion proteins can have any structure and function imparting different properties to the fusion protein. Furthermore, there is no correlation between fusion protein' properties and the structure of the polynucleotide encoding thereof. Thus, the specification fails to provide structure: function correlation present in all members of the claimed genus. No information is provided from which the claimed polynucleotides can be distinguished from other polynucleotide molecules. The specification describes a polynucleotide encoding a 13.6 kD fusion protein containing the rubredoxin, the His-Flag affinity site, the Factor Xa

restriction site and the $A\beta_{1-40}$ amyloid or $A\beta_{1-42}$ amyloid peptides (Figure 2; pages 5-6, 31, 45, SEQ ID NOs: 8, 9). However, the disclosure of two species is not sufficient to represent a variable genus of claimed polynucleotides.

Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim 52 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that plasmid pRUBEX3 is required to practice the claimed invention. The claimed plasmid's sequences are not fully disclosed, nor have all the sequences required for their construction been shown to be publicly known and freely available. As a required element it/they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it/they is/are not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the microorganism(s). See 37 C.F.R. § 1.802.

The specification does not provide a repeatable process for obtaining the microorganism(s) and it is not apparent if the microorganism(s) is/are readily available

to the public. The specification must contain the date that the microorganism(s) was/were deposited, the name of the microorganism(s) and the address of where the microorganism(s) was/were deposited.

If the deposit(s) has/have been made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his/her signature, and registration number, stating that the specific strain(s) has/have been deposited under the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 C.F.R. § 1.808.

If the deposit(s) has/have not been made under the Budapest Treaty, then in order to certify that the deposit(s) meets the criteria set forth in 37 C.F.R. § 1.801-1.809, Applicant(s) may provide assurance of compliance by an affidavit or declaration, or by a statement by an Attorney of record over his/her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit(s) will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a viability statement in accordance with the provisions of 37 C.F.R. § 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 C.F.R. § 1.809 (d) should be added to the specification. See 37 C.F.R. § 1.803-1.809 for additional explanation of these requirements.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 64 and 112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 64 recites "an amyloid". The difference in scope between "an amyloid" and "an amyloid peptide" (claim 75, for example) is unclear rendering the metes and bounds of the claim unascertainable.

Claim 112 is confusing as reciting "A vaccine comprising at least one component selected from the group consisting of: a polynucleotide [ ] and a pharmaceutically acceptable carrier" where it appears "a vaccine comprising a polynucleotide and a pharmaceutically acceptable carrier", for example, is intended.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 45-51, 53-63, 65-87 and 112-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ueno et al. in view of Dobeli et al.

Ueno et al. (EP 0 781 848A2, form PTO-1449 filed June 27, 2001) teach a DNA encoding a fusion protein comprising and N-terminal heat-resistant protein and a C-terminal fused polypeptide (page 2, lines 26-37). Several heat-resistant proteins are mentioned, including *Pyrococcus furiosus* rubredoxin (page 3, lines 6-36, especially line 20). They teach that a heat-resistant protein can be fused directly or indirectly to a DNA encoding a polypeptide (abstract). They teach that linker (spacer) sequence can contain proteolytic cleavage site (page 3, lines 42-52). They teach vectors comprising said fusion proteins and their expression in a host cell with subsequent purification of a polypeptide (page 3, last paragraph; pages 4-12, Examples).

Dobeli et al. (form PTO-1449 filed June 27, 2001) teach a DNA encoding a fusion protein of 133 amino acids comprising a protein tail fused to the N-terminus of either 1-40 β-amyloid peptide or 1-42 β-amyloid peptide. They teach vectors and *E. coli* comprising thereof and production of soluble β-amyloid peptides. They teach that the purification of β-amyloid peptides using NTA column.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the system taught by Ueno et al. for the production of soluble 1-40 β-amyloid peptide or 1-42 β-amyloid peptide. The motivation to produce a β-amyloid peptide is provided by Dobeli et al. who teach the physiological importance of β-amyloid peptide and difficulties in its recombinant production. One of ordinary skill in the art would have a reasonable expectation of success because Ueno et al. teach that the system is useful with any polypeptide and because Dobeli et al. successfully obtained soluble β-amyloid peptide by expressing it as a fusion protein.

It would have been further obvious to use radioactive isotopes routinely used in the art for tracking the proteins as required by claims 61-63, 72-75, 82-87. It is would have been obvious to visually tracking the protein using inherent ability of rubredoxin to bind Fe^{2+} (claims 49, 55, 60, 67, 78). It would have been further obvious to produce a composition such a vaccine comprising the claimed DNA according to a routine use in the art (claims 112-114).

Response to Arguments

Applicant's arguments filed May 20, 2004 have been fully considered but they are not persuasive.

With regard to the 112, 1st paragraph written description rejection, Applicants argue that "The claimed invention is directed to a fusion protein comprising a fusion partner, in this case rubredoxin, fused directly or indirectly to a protein or peptide of interest, together with methods and materials for producing the fusion protein in a host

cell and purifying the fusion protein. Applicants are not required to identify each and every species which encodes for rubredoxin. It is well known in the art that rubredoxins from several different anaerobic organisms have been discovered and characterized" (Remarks, paragraph bridging pages 15-16). It is agreed that Applicants are not required to identify each and every species which encodes for rubredoxin. However, they are required to describe a structure: function relationship common to all species within the genus. The claims are not limited to rubredoxins from anaerobic organisms or any natural source and having a specific structure but to a genus of rubredoxins having any amino acid sequence, i.e. defined by function only. The invention lies in a fusion of a rubredoxin with another polypeptide and the properties of the resulting fusion protein can vary.

While it is acknowledged that the language of the rejected claims is found *en haec vrbis* within the specification, this recitation fails to provide a sufficient description of the claimed genus of polynucleotides encoding fusion proteins as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from

others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly with the claimed genus of fusion proteins comprising rubredoxin, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus. Furthermore, there is no disclosure of the correlation between the fusion protein and the structure of the DNA encoding thereof.

Applicants argue that "the claimed invention is not directed to a particular polynucleotide sequence; rather, the claims are directed to a construct describing a particular way of combining types of sequences (i.e. a rubredoxin fusion protein comprising an N-terminal rubredoxin constituent and a C-terminal fused polypeptide of interest). The claims are therefore directed to a novel combination of known types of sequences, and are not drawn to a particular sequence. As such, Applicants are not required to disclose every possible sequence that can be used interchangeably in the claimed polynucleotide constructs. The novelty of the invention does not lie in the particular sequence used, but lies in the structure of the construct" (page 18, last paragraph, emphasis added). This is not persuasive because the rejection is made exactly because "the structure of the construct" is not described. Applicants did not identify characteristics that impart novelty to a fusion protein comprising a rubredoxin and do not disclose the correlation between said fusion protein and the DNA encoding thereof. With regard to claims 64 and 82-87 Applicants argue that "Applicants have not

only sufficiently provided representative β-amyloid, but have also indicated that numerous β-amyloid are widely known by a skilled artisan at the time of the invention. As argued above, Applicants are not required to list each and every single working example of β-amyloid" (page 20). As explained above, β-amyloid is a chemical compound and its description by function only is insufficient.

With regard to the 112, 1st enablement rejection of claim 52, Applicants argue that "Applicants have also provided, in Figure 1, a schematic of the vector pRUBEX3, including the Multiple Cloning Region (MCR) and the nucleotide sequence of a portion of pRUBEX3 together with the amino acid sequence encoded. Not only is pRUBEX3 defined and exemplified in Figure 1, Applicants have also provided in Example 1, the method to yield pRUBEX3 (Specification, Example 1, page 25, line 23 to page 28, line 24; **with emphasis** on page 28, lines 23-24). Thus, the specification has been disclosed in a manner that one skilled in the art would be able to practice the invention without an undue amount of experimentation (emphasis added). See In re *Colianni*, 561 F.2d at 224,195 U.S.P.Q. at 153 ; *see also M. P.E.P* §2164.02" (page 22). This is not persuasive because as admitted by Applicants only a schematic of the vector pRUBEX3 is described and only a portion of the vector's sequence is disclosed. Therefore, it would involve an undue experimentation to make this vector.

With regard to the 103(a) rejection, Applicants argue that "The Dobeli et al. paper, where they made a 13.8 kD fusion with the amyloid, is not soluble and goes into the inclusion bodies. Further, nowhere in the reference does it teach or suggest an iron containing nucleotide having red color for easy tracking. Not only is there no suggestion

or motivation, the Dobeli et al. reference teaches away from the presently claimed invention. The Dobeli reference teaches a chemical cleavage of beta-amyloid from fusion which causes side reactions. The Ueno et al. reference does not teach or suggest the use of any β-amyloid. Further the Ueno disclosure does not teach rubredoxin constituent that is soluble, nor does it teach a rubredoxin constituent that goes into the inclusion bodies. Thus, even if all the references were to be combined, there would be no teaching or suggestion of the claimed invention. Prior to the present application, no one had described that rubredoxin was a suitable fusion partner for creating soluble expression products that are also colorimetric. Further evidence of the surprising utility of rubredoxin in this context is that the previously mentioned article published in Kohli et. al., where skilled researcher at Novartis Pharma were surprised to "discover" the subject expression system, not realizing that the invention had already been made at least five years earlier by the present applicants" (paragraph bridging pages 25-26). This is not persuasive because the Ueno et al. reference does teach a polynucleotide comprising a fusion protein comprising a rubredoxin and a polypeptide of interest, *supra*. The Ueno et al. reference does not specifically teach a fusion with a β-amyloid peptide. However, Dobeli et al. teach the importance of β-amyloid peptide in neuropathological conditions, definitely providing a motivation to obtain it in purified form. As a secondary reference in a 103(a) rejection, the Dobeli et al. does not need to teach the same invention but only to make it obvious, i.e. to provide motivation to use β-amyloid peptide as a polypeptide of interest in the Ueno et al. reference. With regard to Kohli et al. reference, it discloses a fusion protein comprising a *Thermatoga martina*

rubredoxin with another polypeptide. Kohli et al. do not use a β-amyloid peptide as a polypeptide of interest, it is published after the filing date of the instant invention and as such does not aid in obviating the outstanding rejections of the instant claims.

The 102(b) rejection over Menon et al. is withdrawn because as argued by Applicants (page 24), it does not disclose the rubredoxin as a constituent of the fusion protein not enabling one of skill in the art to make the claimed fusion protein.

The previous 112, 2nd paragraph rejection is withdrawn in view of the amendment.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

August 19, 2004